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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/117,218	01/11/1999	SUSANNE M. BROWN	117-261	3436

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/117,218	BROWN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/04/02 in Paper No. 16 has been entered.

Claims 23-32 are pending in the present application and they are examined on the merits herein.

Claim Objections

Claim 24 is objected to because of the following informalities: the terms " where in" on line 1 of the claim should be one word - - wherein - -. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 23 and its dependent claims, it is unclear what is encompassed by the phrase "a mutant herpes simplex virus comprising a non-functional gene, wherein said non-functional gene consists essentially of a non-functional gamma 35.4 gene". Do Applicants intend to claim a method of treating a non-neuronal cancer using a mutant herpes simplex virus containing a larger non-functional gene and within this non-functional gene is the non-functional gamma 35.4 gene? Or a method of treating a non-neuronal cancer using a mutant herpes simplex virus containing only a non-functional gamma 35.4 gene? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 23-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994; Cited previously).

Due to the open language of the term "comprising", the instant claims are drawn to a method of treating a non-neuronal cancer using a mutant herpes simplex virus that contains other non-functional genes as long as it contains a non-functional gene consisting essentially of a non-functional gamma 35.4 gene.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals

suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67). Therefore, Martuza et al. clearly anticipate the instantly claimed invention.

It should be noted that the U.S. Patent No. 6,139,834 of Martuza et al. has an effective filing date of June 23, 1994 because of the supports found in column 3, lines 52-58; column 12, lines 6-7; column 15, lines 41-50 and other embodiments contained in the U.S. Patent No. 5,585,096 of Martuza et al.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on September 04, 2002 in Paper No. 16 (pages 4-5) have been fully considered.

Applicants argue that Martuza teaches the modification of the ribonucleotide reductase gene as being an essential feature of his invention, and that Martuza indicates that the ribonucleotide reductase negative mutants are avirulent and, as such, the inclusion of a modified ribonucleotide reductase gene is "essential to a therapeutic vector" (col. 6, lines 40-45 of the Martuza's patent). Therefore, Applicants believe that Martuza teaches away from using a mutant having a gamma34.5 gene mutation without a modification in the ribonucleotide reductase gene for non-neuronal treatment. Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, as written due to the open language of the term "comprising", the instant claims are drawn to a method of treating a non-neuronal cancer using a mutant herpes simplex virus that contains other non-functional genes as long as it contains a non-functional gene consisting essentially of a non-functional gamma 35.4 gene. As such, the instant claims still read over the teachings of Martuza et al.

Secondly, there is nowhere in the Martuza's patent indicating or suggesting that the modification of the ribonucleotide reductase gene as being an essential feature for killing any tumor cells, including non-neuronal tumor cell, which is the main feature of the presently claimed invention. The passage in col. 6, lines 40-45, in the Martuza's patent cited by Applicants merely indicates the herpes simplex virus RR- mutants are attenuated for neurovirulence and less likely to propagate in the event of a fever in the infected host, and that these characteristics are essential to a therapeutic vector which must be of attenuated neurovirulence and amenable to antiviral therapy in the event of viral encephalitis. The herpes simplex virus mutant deficient in only the gamma34.5 gene such as R3616 is already attenuated for neurovirulence and retains the wild-type level of sensivitity to acyclovir, and therefore such herpes simplex virus mutant has the the same characteristics essential of a therapeutic vector (see col. 6, lines 49-66). Therefore, Martuza does not teach away from using a mutant having a gamma34.5 gene mutation without a modification in the ribonucleotide reductase gene for non-neuronal treatment.

Accordingly, claims 23-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Martuza et al. for the reasons set forth above.

Claims 23-26, 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Roizman et al. (U.S. Patent No. 6,340,673).

Roizman et al. teach using an HSV-1 virus with a specific mutation in the gamma 35.4 gene to treat cancer and tumorogenic diseases both in the CNS and in all other parts of the body in a mammal including human, not necessarily limited to tumors of the CNS (see col. 5, lines 63-66; col. 9, lines 50-61; and the claims). Roizman et al. further teach direct injection of the virus into the tumor or intratumorally, and that an exemplified HSV-1 virus with a specific mutation in the gamma 35.4 gene is the recombinant virus R3617 or R3616 lacking 1kb of DNA in each copy of the gamma 34.5 gene (see Table 1 of col. 17; Fig. 2). Roizman et al. also teach that infection of cells of neuronal origin with mutants incapable of expressing the gamma 34.5 gene resulted in shutoff of cellular protein synthesis, whereas infection of cells of non-neuronal origin with wild type or mutant viruses resulted in sustained protein synthesis and production of infectious progeny (col. 18, lines 10-15).

Accordingly, the teachings of Roizman et al. meet every limitation of the instant claims, and therefore the reference anticipates the instant claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994; Cited previously) in view of either MacLean et al. (J. Gen. Virol. 72:631-639, 1991, Cited previously) or Brown et al. (WO 92/13943 with a publication date of August 20, 1992; PTO-1449, IDS) and Markert et al. (Neurosurgery 32:597-603, 1993; IDS).

Due to the open language of the term "comprising", the instant claims are drawn to a method of treating a non-neuronal cancer using a mutant herpes simplex virus that contains other non-functional genes as long as it contains a non-functional gene consisting essentially of a non-functional gamma 35.4 gene.

With respect to a method for killing tumor cells in a subject via intratumoral injection of mutant herpes simplex virus, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a

pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67).

Martuza et al. do not teach a method of killing tumor cells in a subject using the mutant herpes simplex virus wherein there is a deletion from 0.7 to 0.8 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome, or wherein the mutant herpes simplex virus is strain 1716.

Both MacLean et al. and Brown et al. disclose HSV-1 mutant 1716 and they both teach that strain 1716 contains a 759 bp deletion in the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See abstract and

Fig. 3 on page 634 of MacLean et al.; page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence for strain 1716 comparing to the parental wild type strain.

Markert et al. teach a herpes simplex virus-1 called R3616 with decreased neurovirulence (See abstract) and the virus contains a 1kb deletion in the γ34.5 gene (page 598, column 1, bottom of third paragraph). Markert et al. further teach that R3616 possesses antineoplastic effects and it significantly prolonged average survival without producing premature encephalitic deaths in a nude mouse intracranial glioma model (See abstract).

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to substitute any of the mutant herpes simplex virus utilized in the method disclosed by Martuza et al. with mutant virus strain 1716 taught by MacLean et al. and Brown et al., and one of ordinary skilled in the art would have expected to successfully killing tumor cells in a subject via an intratumoral route of delivery. This is because it was well known in the art that mutant herpes simplex virus having a deletion in the γ34.5 gene has reduced non-neurovirulence and still possesses anti-neoplastic effects as exemplified by the teachings of Markert et al. and Martuza et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

R sponses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on September 04, 2002 in Paper No. 16 (pages 5-6) have been fully considered.

Applicants basically argue that none of the secondary references teaches that Martuza's mutant, which contain as an essential element a modification of the ribonucelotide reductase gene, should be excluded. Applicants' arguments are respectfully found to be unpersuasive for the same reasons set forth in the Response to the rejection of claims 23-30 above.

Accordingly, claims 23 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. in view of either MacLean et al. or Brown et al. and Markert et al. for the reasons already set forth above.

Claims 23, 27 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. Patent No. 6,340,673) in view of Martuza et al. (U.S. Patent No. 6,139,834) and either MacLean et al. or Brown et al.

Roizman et al. teach using an HSV-1 virus with a specific mutation in the gamma 35.4 gene to treat cancer and tumorogenic diseases both in the CNS and in all other parts of the body in a mammal including human, not necessarily limited to tumors of the CNS (see col. 5, lines 63-66; col. 9, lines 50-61; and the claims). Roizman et al. further teach direct injection of the virus into the tumor or intratumorally, and that an exemplified HSV-1 virus with a specific mutation in the gamma 35.4 gene is the recombinant virus R3617 or R3616 lacking 1kb of DNA in each copy of the gamma 34.5

gene (see Table 1 of col. 17; Fig. 2). Roizman et al. also teach that infection of cells of neuronal origin with mutants incapable of expressing the gamma 34.5 gene resulted in shutoff of cellular protein synthesis, whereas infection of cells of non-neuronal origin with wild type or mutant viruses resulted in sustained protein synthesis and production of infectious progeny (col. 18, lines 10-15).

Roizman et al. do not specifically teach a method for treating mesothioma, ovarian carcinoma, bladder cancer or melanoma using the recombinant virus R3617 or R3616. Nor do Roizman et al. specifically teach the use of the mutant herpes simplex virus in which the deletion in the gamma 35.4 gene is from 0.7 to 0.8 kb or the use of the mutant herpes simplex virus strain 1716.

However, at the effective filing date of the present application, Martuza et al. already teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1 and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). Additionally, at the effective filing date of the

present application, both MacLean et al. and Brown et al. disclose HSV-1 mutant 1716 and they both teach that strain 1716 contains a 759 bp deletion in the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See abstract and Fig. 3 on page 634 of MacLean et al.; page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence for strain 1716 comparing to the parental wild type strain.

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to use the recombinant virus R3617 or R3616 lacking 1kb of DNA in each copy of the gamma 34.5 gene of Roizman et al. to lyse or kill mesothioma, ovarian, bladder or melanoma cells in light of the teachings of Martuza et al. One of ordinary skilled artisan would have been motivated to do so because Martuza et al. already teach that the mutant herpes simplex virus comprising a 1-kB deletion in both copies of the γ34.5 gene is capable of killing mesothioma, ovarian, bladder or melanoma cells. It is further noted that the mutant herpes simplex virus taught by Maruza et al. further contains an alteration in the ribonucleotide reductase gene, which is not essential to the killing of non-neuronal cancer cells, but mainly for the purpose of reducing the possibility of the mutant herpes simplex virus to revert to the wild-type virus (col. 5, lines 40-42).

Similarly, it would also have been obvious and within the scope of skill for an ordinary skilled artisan to substitute the mutant herpes simplex virus utilized in the method disclosed by Roizman et al. with the mutant virus strain 1716 taught by either MacLean et al. or Brown et al. One of ordinary skilled in the art would have been

motivated to carry out the modification and expected to successfully killing tumor cells in a subject via an intratumoral route of delivery using the mutant virus strain 1716 because it was already known in the art that a mutant herpes simplex virus having a deletion in the γ34.5 gene has reduced non-neurovirulence and still possesses anti-neoplastic effects as exemplified by the teachings of Roizman et al. and Martuza et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Tiffiany Tabb, whose telephone number is (703) 605-1238.

Quang Nguyen, Ph.D.

Gerald D. Leffers
PATENT EXAMINER
Gerald G. Leffers Jr.
A. U. 1636